

A Compliance by Australasian Paediatricians with the 2009 NASPGHAN-ESPGHAN Guideline for the Diagnosis and Management of Gastro-Oesophageal Reflux in Children

Sunita Shanmuganathan^{1*}, Emily Horsley^{2,3}, Elizabeth Argent², Paolo Quitadamo⁴, Annamaria Staiano⁴ and Usha Krishnan^{5,6}

¹Department of Paediatric Oncology, University College Hospital London 235 Euston Road, London NW1 2BU, England

²Department of General Paediatrics, Sydney Children's Hospital, Randwick, New South Wales, Australia

³Department of Paediatrics, Manly and Mona vale Hospital, New South Wales, Australia

⁴Department of Paediatrics, University "Federico II", Naples, Italy

⁵Department of Paediatric Gastroenterology, Sydney Children's Hospital, Randwick, New South Wales, Australia

⁶School of Women's and Children's Health, University of New South Wales, Randwick, New South Wales, Australia

Abstract

Objective: To investigate the current approach of Australia and New Zealand paediatricians to children with gastro-oesophageal reflux symptoms, comparing practice against the NASPGHAN-ESPGHAN guideline.

Method: Prospective, multicentre study was carried out in Australia and New Zealand between November 2012 and June 2013. Questionnaires were distributed, consisting of multiple choice case reports like issues, concerning clinical management, the use of diagnostic tools and the treatment options for Gastro-Oesophageal Reflux Disease (GORD) in infants, children and adolescents, via email to a selected email list of paediatricians across the country.

Results: 53 paediatricians completed the study questionnaire. 71.7% diagnosed GORD based on symptomatology, irrespective of the child's age. 45.2% prescribed Proton Pump Inhibitors (PPIs) to children of all ages, whilst 39.6% prescribed mainly to infants. In infants, 39.6% of these prescriptions were for uncomplicated recurrent regurgitation and vomiting and 66% were for unsettled behaviour, without specific testing. 50% of prescribed PPIs in children older

than 5 years of age were for vomiting and heartburn, without investigating. 30.7% would discontinue PPIs abruptly and only 50.9% were aware that the most frequent adverse event of PPI therapy in infants is lower respiratory tract infection. 26.4% of paediatricians wrote > 15 PPI prescriptions during the last 6 months.

Conclusion: The results of this survey showed varied response on the management of GORD in Australasia. Paediatricians in Australasia were overprescribing PPIs in infancy for presumed symptoms of GORD in the absence of diagnostic evidence.

***Corresponding Author:** Sunita Shanmuganathan, Department of Paediatric Oncology, University College Hospital London 235 Euston Road, London NW1 2BU, England; Tel: +442074567890; Fax: +44 (0)20 3447 1841; E-mail: atinus@doctors.org.uk

Introduction

Gastro-Oesophageal Reflux (GOR), a normal physiological process that occurs in healthy infants and children, refers to the

passage of gastric contents into the oesophagus with or without regurgitation. Gastro-Oesophageal Reflux disease (GORD) refers to GOR associated with pathological consequences, such as esophagitis, nutritional compromise or respiratory symptoms. In 2007, an international panel of 9 paediatric gastroenterologists and 2 epidemiologists sought to develop an international consensus on the definition of GORD in the paediatric population [1]. It was unanimously agreed that GORD in the paediatric population is present when reflux of gastric contents is the cause of troublesome symptoms and/or complications. Amongst other things agreed upon was that these symptoms vary with age and are noted to be troublesome when they have an adverse effect on the wellbeing of the paediatric patient. Following this, in October 2009, the North American Society for Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) published new evidence based clinical practice guidelines for the diagnosis and management of GORD in the paediatric population to improve uniformity of practice and quality of patient care [1]. A recent prospective, multicentre study performed in 10 European countries to investigate the current approach of European General Paediatricians to children with GORD symptoms, evaluating the implementation of the 2009 NASPGHAN-ESPGHAN guidelines and to assess the Proton Pump Inhibitors (PPIs) prescribing patterns, showed that the majority of paediatricians were unaware of the guideline [2]. In Australia, most pediatricians tend to follow the ESPGHAN-

NASPGHAN guideline for most common pediatric gastrointestinal conditions. Based on this fact and the results of the European study, we sought to investigate the current approach amongst paediatricians in Australia/New Zealand to infants, children and adolescents with GORD symptoms.

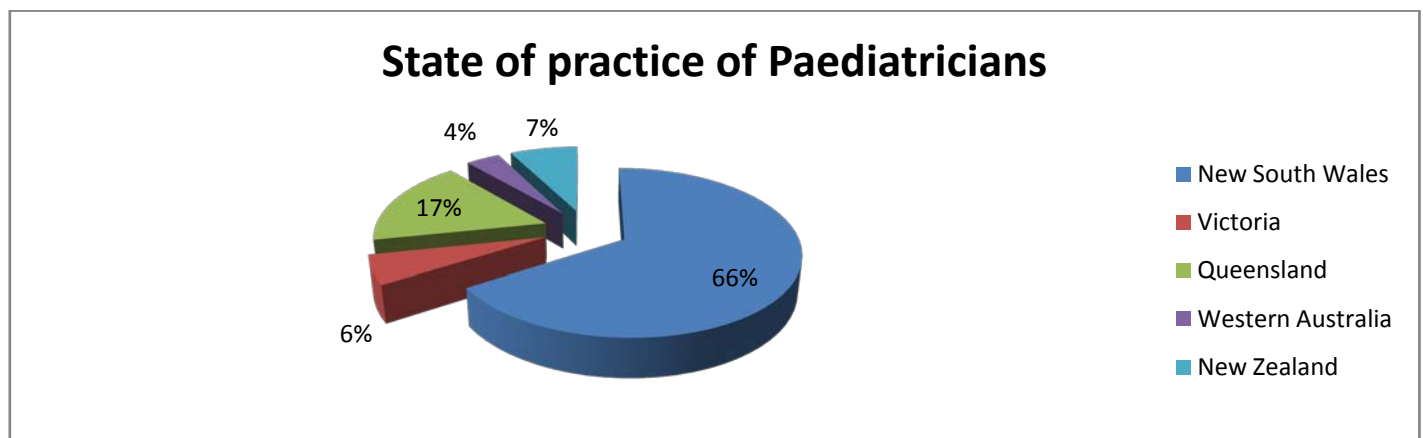
Method and Materials

This prospective, multicentre study was carried out in Australia and New Zealand. The study period was between November 2012 and June 2013 and was approved by the Human Research Ethics Committee (HREC). A questionnaire was emailed to a list of paediatricians across the country. The questionnaire used was identical to the questionnaire designed for the European study. It consisted of 14 multiple choice case report like issues, concerning clinical management, the use of diagnostic tools and the treatment options for GOR/GORD in infants, children and adolescent. All responses were confidential. Comparison was made to the results of the European study. Results were analysed using Chi-square test with Yates' correction. A $p < 0.05$ was used for significance.

Results

A total of 407 emails were sent to paediatricians in Australia and New Zealand. The number of responders was 53 (13%), 66% of whom were practising in New South Wales (Figure 1). This response rate was significantly lower than the 42% responders (567/1350) in the European study ($p < 0.001$).

Figure 1:



Diagnostic Tools

Majority of the paediatricians, 38/53 (71.7%) diagnosed GORD through a history of presumed reflux symptoms, irrespective of the age of the child. 3 (5.7%) used specific testing (upper GI endoscopy and/or oesophageal pH monitoring), 1 (1.9%) used barium contrast radiography. Only 11 (20.8%) diagnosed GORD correlating the symptoms with the age of the child. These results are similar to that of the European study (18.7%) ($p=0.85$).

Therapeutic Options

41/53 (77%) of the involved paediatricians consider Proton Pump Inhibitors (PPIs) the mainstay of treatment for GORD which was in accordance with the guideline. 67% of the paediatricians in the European study considered PPIs the mainstay of treatment. 7/53 (13.2%) considered gastric acid buffering agents the mainstay and 3/53 (5.7%) used Histamine-2 receptor antagonist. No paediatricians in this study considered mucosal surface barriers or pro kinetics,

compared to 7.3% and 6.3% respectively in the European study. 2/52 (3.8%) paediatricians in this study chose to skip this question. With regards to prescribing PPIs according to the child's age, 24/53 (45.2%) of paediatricians prescribed PPIs to children of all ages, whilst 21/53 (39.6%) prescribed mainly to infants in their practice. 4/53 (7.8%) prescribed mainly to children between the ages of 1 to 5 and 2/53 (3.7%) mainly to children older than 12 years (Figure 2).

21/53 (39.6%) of paediatricians prescribed PPIs in infants younger than 1 year of age with uncomplicated recurrent regurgitation and vomiting in the absence of diagnostic evidence. This result was similar to that of the European study (36.2%) ($p=0.72$). 31/53 (58.5%) never prescribed PPIs in this situation (Figure 3). In infants younger than 1 year of age with unexplained crying and/or distressed behaviour, 35/53 (66%) of paediatricians prescribed PPIs. This number was significantly higher than the European study, where only 38.9% of paediatricians prescribed PPIs in this situation ($p<0.002$) (Figure 4).

Figure 2:

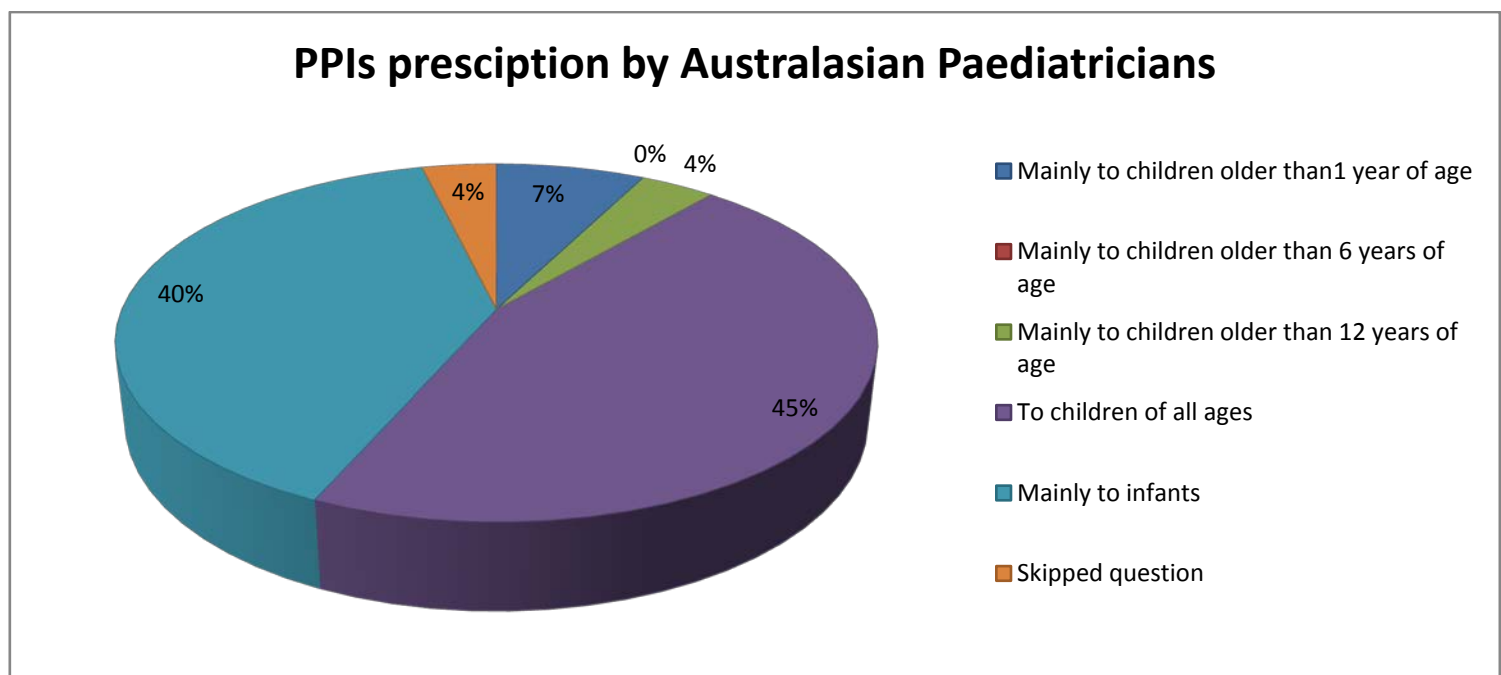


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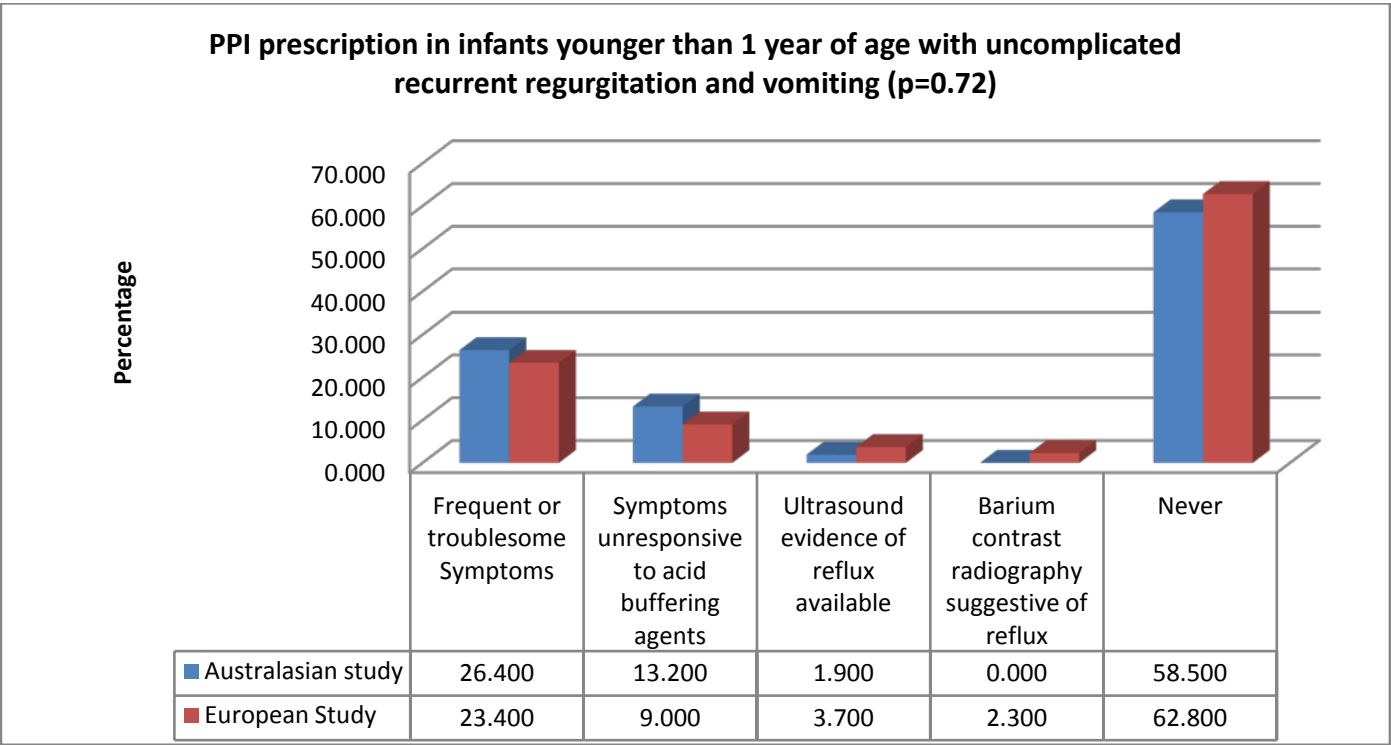
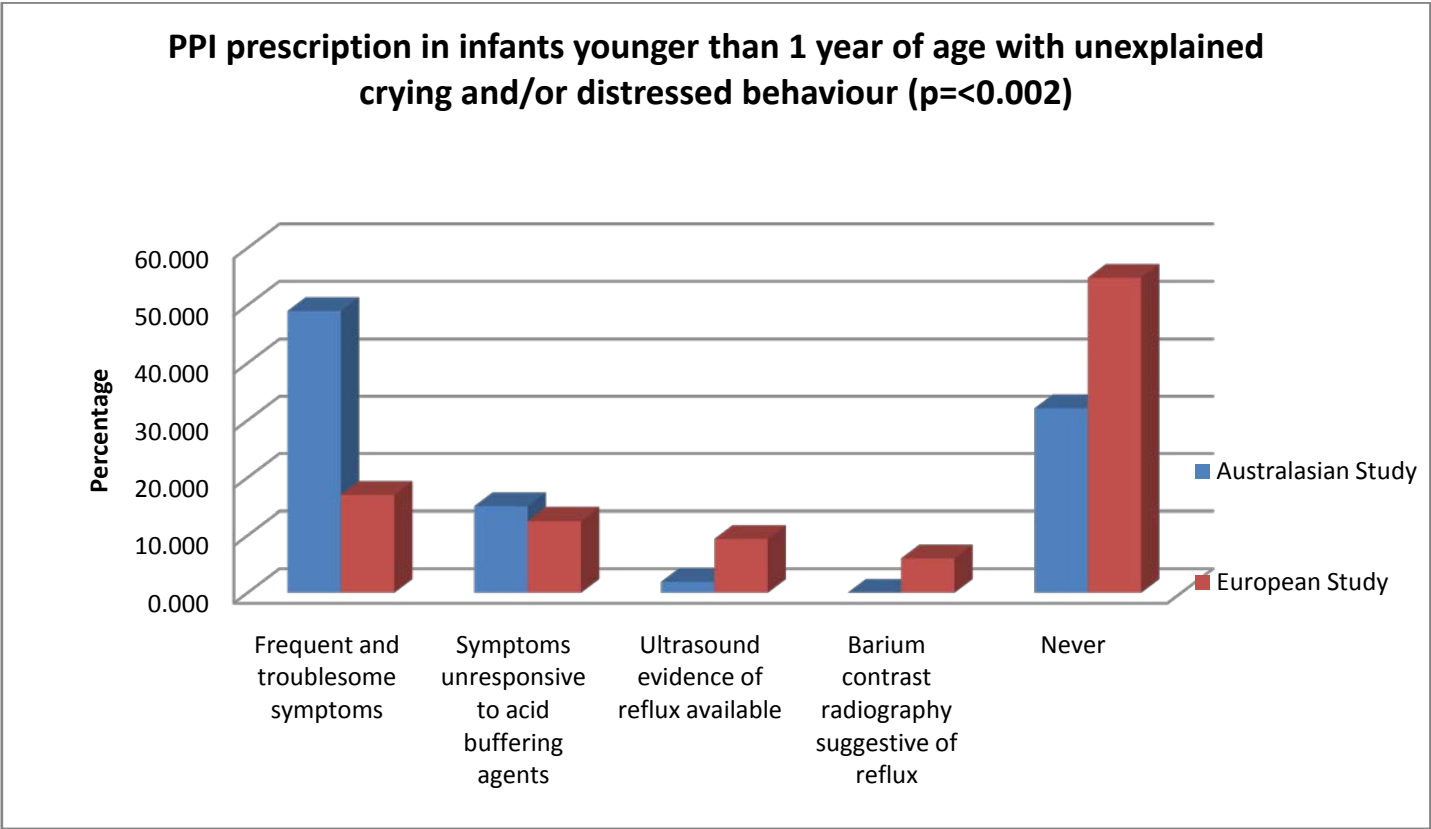


Figure: 4



In children older than 5 years with heartburn and vomiting and in adolescents with heartburn and chest pain, 27/53 (51%) paediatricians initiate a PPI as first line without further investigation of symptoms. 14/53 (26.4%) would carry out specific testing (upper GI endoscopy) prior to commencing a PPI. When recommending which group of children would benefit from a 2 to 4 week trial of PPI in older children with typical reflux symptoms, only 4/53 (7.5%) of paediatricians in this study suggested that older children and adolescent with chronic heartburn would benefit from this, compared to 34.2% in the European trial. 29/53 (54.7%) of paediatricians in this study would recommend a 2 to 4 week trial of PPI in children of all ages with typical reflux symptoms.

With regards to testing children of any age with respiratory symptoms suspected to be GORD related, all agreed that oesophageal and gastric ultrasonography had no role, however only 12/53 (22.6%) would perform a pH or impedance monitoring as recommended in the guideline. 9/53(%) would perform an upper GI endoscopy, 15/53(%) would request a barium contrast radiography whilst 17/52 (32.1%) would perform no testing but instead trial PPIs for 2 to 4 weeks (Figure 5). 19/53 (35.8%) of paediatricians surveyed would

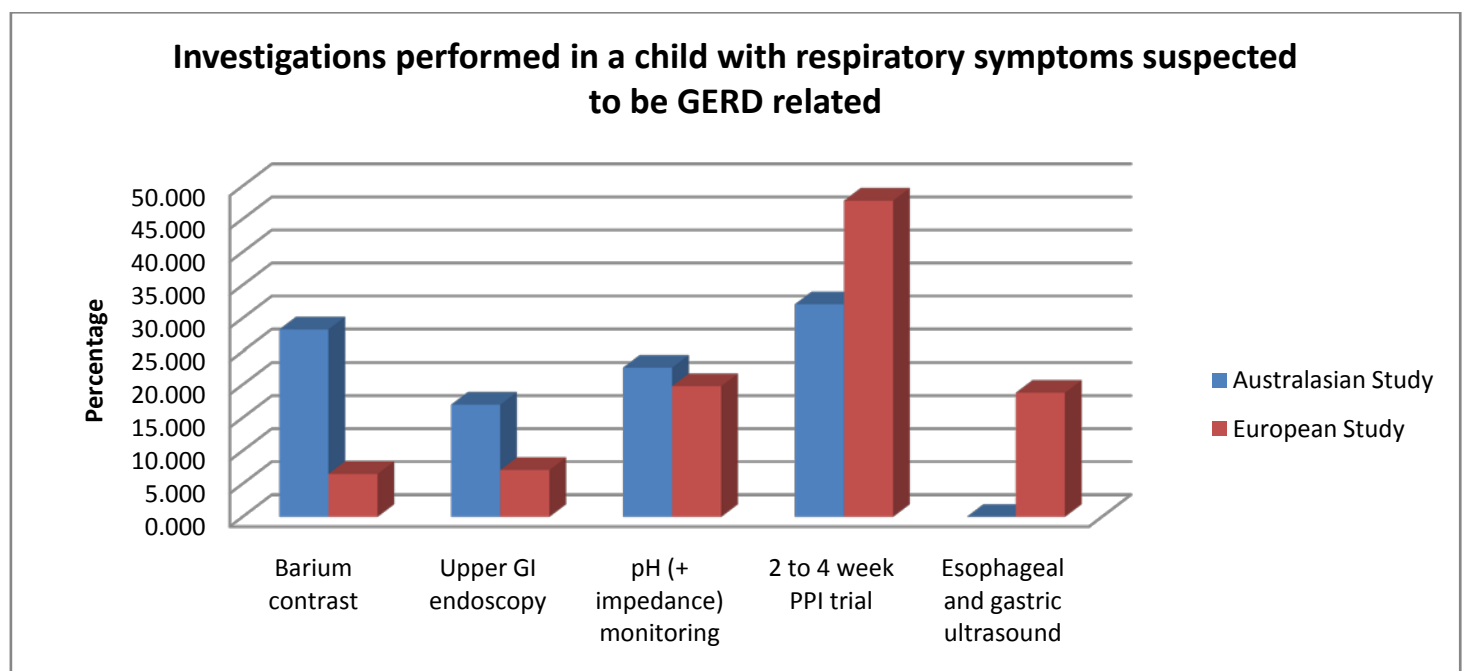
perform an upper GI endoscopy in a child aged 5 years or over with respiratory symptoms suspected to be GORD related and a similar number, 16/53 (30%) thought this would be necessary in the same age group with recurrent vomiting and heartburn.

8/53 (15%) thought a child age 12 years and over with recurrent vomiting and heartburn might benefit from a upper GI endoscopy. Interestingly, 4/53 (7.5%) suggested that children of all ages with suggestive reflux symptoms would benefit from gastroscopy. The most frequent adverse events of PPI therapy in infants are lower respiratory tract infection [1]. 27/53 (50.9%) of paediatricians in this study was aware of this fact, as oppose to 68% in the European study.

36/53 (67.9%) of paediatricians in this study appropriately weaned children of PPI whilst 16/53 (30.7%) would discontinue it abruptly. This is in comparison to 49.6% of paediatricians in the European study that would discontinue PPI abruptly.

There was a wide range of the number of PPI prescriptions made during the last 6 months. 26/53 paediatricians wrote <5 PPIs prescription in the preceding 6 months whilst 14/53 (26.4%) prescribed >15 PPIs.

Figure 5:



Discussion

GORD is a frequently occurring condition in childhood. In view of this, a consensus on the management of this condition will improve quality of care, achieve better outcomes and subsequently decrease overall health costs. In Australia, two PPIs made the top ten most prescribed PBS medications in 2011-12 and 15.2 million script volumes were written for drugs for GORD. Esomeprazole alone cost the government A\$168million [3]. The NASPGHAN-ESPGHAN guideline was developed in 2009 to provide paediatricians and paediatric subspecialists with an evidence based clinical practice guidelines for the evaluation and management of GORD [1]. To date, there is no similar guideline in Australasia; however Australasian pediatricians tend to follow the ESPGHAN-NASPGHAN guidelines for most common pediatric gastrointestinal conditions.

Previous studies have found that the majority of paediatricians generally diagnose GORD based on a clinical history of reflux symptoms without specific testing, irrespective of the age of the child. This is despite there being no validated symptom questionnaire for GORD in all age groups and also the fact that the guidelines state that symptoms and signs associated with reflux are nonspecific, except for heartburn and chest pain in the older child and adolescent [1]. 45.8% of paediatricians in the European Study carried out in 2011 diagnosed GORD on the basis of a history of reflux without investigations [2]. A survey amongst French Paediatricians in 2012 reported 59% [4] whilst a survey amongst North American paediatricians documented 31% of paediatricians having this diagnostic approach [5]. Our survey corroborated these previous findings though at a significantly higher rate of 71.8%. Only a small number of paediatricians in this study (20.8%) made a diagnosis of GORD depending on the age of the child, in keeping with the NASPGHAN-ESPGHAN guideline.

For healing of erosive esophagitis and relief of GORD symptoms, PPIs are superior to Histamine 2 receptor antagonist and both medications are superior to placebo [1]. In this study, 80% of paediatricians agreed PPI was the

mainstay of treatment for GORD. However PPIs are often overprescribed where not clinically indicated and in the absence of specific evidence of reflux oesophagitis. Putnam in his paper "Stop the PPI express, they don't keep babies quiet" highlighted the overuse of PPIs [6]. Other studies have also reported similar overuse [7, 8]. The NASPGHAN-ESPGHAN guideline recommends that PPIs should not be prescribed in patients younger than 1 year of age in the absence of specific evidence. A multicentre, double-blind, randomized, placebo-controlled trial in 2008 assessing the safety and efficacy of PPIs (lansoprazole) in infants with symptoms of GORD detected no difference in efficacy between lansoprazole and placebo for symptoms attributed to GORD in infants age 1 to 12 months [9]. Davidson et al., in their study to evaluate the efficacy and safety of esomeprazole for the treatment of GORD in neonates showed that esomeprazole was well tolerated, reduced oesophageal acid exposure and the number of acidic reflux events in neonates compared to placebo, however, the signs and symptoms of GORD traditionally attributed to acidic reflux in neonates were not significantly altered [10]. Despite these evidences, 66% of paediatricians in this study prescribed PPIs in infants under the age of 1 with unexplained crying and distressed behaviour and 39.6% prescribed PPIs in the same age group for uncomplicated recurrent regurgitation and vomiting in the absence of diagnostic evidence. Parental education, reassurance and anticipatory guidance are the recommended management as opposed to PPIs in the uncomplicated recurrent regurgitation and vomiting [1]. In infants with unexplained crying, reflux is not noted to be a common cause of symptoms in an otherwise healthy infant. Following exclusion of other causes, an empiric trial of extensively hydrolysed protein based formula can be commenced [1]. There is no evidence to support the empiric use of acid suppression in the treatment of the irritable infant [1]. Typical symptoms of reflux in children older than 5 years of age are heartburn and vomiting whilst in adolescents, typical reflux symptoms are heartburn and chest pain. In children greater than 5 years of age and adolescents, PPIs are recommended as an empiric therapeutic trial [1].

Approximately half of paediatricians surveyed in our study would initiate an empiric PPI trial in these circumstances with no further investigations. The NASPGHAN-ESPGHAN guideline states that a 2 to 4 week trial could be recommended for older children and adolescent with chronic heartburn, yet only 7.5% of paediatricians in this study followed this recommendation.

In our study, investigations for the diagnosis of GORD proved to have the most varied response. All respondents agreed that ultrasound had no role in the routine evaluation of GORD in children. This is in contrast to the European study, where ultrasound is still being used to diagnose GORD. Studies have repeatedly shown that the use of ultrasound in the diagnosis of GORD has high specificity but low sensitivity [11, 12]. Currently, combined multiple oesophageal impedance pH recording according to the guidelines is considered to be the gold standard for the evaluation of GOR related symptoms [1]. Despite this we found that only 22.6% of paediatricians in our study would perform a pH (+/-impedance) monitoring in a child with respiratory symptoms suspected to be GORD related. Whilst this could be because the paediatricians were unaware of the guidelines, it could also be because this investigation is not readily available in all centres, there are no normative data in children and there is no outcome studies based on results on pH impedance monitoring in children unlike those in adults. In our study 28.3% would perform barium contrast radiography only despite its low sensitivity and specificity for diagnosing GORD [13], a third would commence a 2 to 4 week PPI empiric trial without investigation for respiratory symptoms even in the absence of typical GORD symptoms. Only 17% would refer to a gastroenterologist for an upper GI endoscopy for exclusion of reflux oesophagitis and for excluding other diseases, which might mimic reflux like eosinophilic oesophagitis.

Opinions were divided in which children would benefit from an upper GI endoscopy. 36% would perform an upper GI endoscopy in a child aged 5 years and over with respiratory symptoms suspected to be GORD related, whilst

30% would perform upper GI endoscopy in a child aged 5 years and over with recurrent vomiting and heartburn. In this situation, the NASPGHAN-ESPGHAN guideline recommends that a child with recurrent vomiting and heartburn would benefit from an upper GI endoscopy. Endoscopic biopsy is important to identify reflux oesophagitis or rule out other causes of esophagitis, and to diagnose and monitor Barrett's oesophagus and its complications [1].

The biggest limitation of this study was the poor response rate. This may have resulted in both a measurement bias and failure to fully survey the full paediatrician population. However previous studies on similar investigations have also documented a low response rate [2, 3, 4, 14]. At the same time the main strength of this is the fact that this is the first prospective multicentre study in Australia and New Zealand looking at approach of Paediatricians to children with gastro-oesophageal reflux symptoms, and comparing current practice against the NASPGHAN-ESPGHAN Guidelines.

In summary, our study showed lack of uniformity in the management of GORD amongst the Australasian paediatricians. Australasian paediatricians were overprescribing PPIs in infants under the age of 1. There was overuse of investigations with poor specificity and sensitivity like barium contrast studies and underuse of more sensitive/specific investigations like pH+/-impedance monitoring and gastroscopy. Education regarding currently available evidence based guidelines and recommendations for diagnosis and management of GORD should be undertaken to improve quality of care, reduce unwanted side effects and decrease the cost of health care. In the future following a suitable education program about the guidelines amongst the paediatricians, we hope to conduct a second phase in order to assess for a change in paediatrician management of GOR/GORD.

References

1. Pediatric Gastro-Oesophageal Reflux Clinical Practice Guidelines: Joint recommendations of the North American Society for Pediatric Gastroenterology,

- Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric gastroenterology, Hepatology, and Nutrition (ESPGHAN). *Journal of Pediatric Gastroenterology and Nutrition* 2009 Oct;49(4):498-547
2. Paolo Quitadamo, M.D., Alexandra Papadopoulou, M.D., Tobias Wenzl, M.D., Vaidotas Urbonas, M.D., Frank Kneepkens, M.D., Enriqueta Roman, M.D., Rok Orel, M.D., Daniela Jojkić Pavkov, M.D., Jorge Amil Dias, M.D., Yvan Vandenplas, M.D., Aco Kostovski, Erasmo Miele, M.D., Alberto Villani, M.D., Annamaria Staiano, M.D. European Pediatricians' Approach to Children with Gastro-Oesophageal Reflux Symptoms: Survey on the Implementation of 2009 NASPGHAN-ESPGHAN Guidelines; *JPGN Journal of Pediatric Gastroenterology and Nutrition* 2014;58(4):505-9
3. http://medicinesaustralia.com.au/files/2010/11/MAFactsBook3_UpdateNov13.pdf
4. Martigne L, Delaage PH, Thomas-Delecourt F et al. Prevalence and management of Gastro-Oesophageal Reflux disease in children and adolescent: a nationwide cross-sectional observational study. *Eur J Pediatr* 2012 Dec;171(12):1767-73
5. Diaz DM, Winter HS, Colletti RB et al. Knowledge, attitudes and practice styles of North American pediatricians regarding Gastro-Oesophageal Reflux disease. *J Pediatr Gastroenterol Nutr* 2007 Jul;45(1):56-64.
6. Putnam PE. Stop the PPI Express: They Don't Keep Babies Quiet! *J Pediatr* 2009;154(4):475-476
7. M.N. Choudhry, H. Soran, and H.M. Ziglam. Overuse and inappropriate prescribing of proton pump inhibitors in patients with *Clostridium difficile*-associated disease. *QJM* 2008 Jun;101(6):445-448
8. Rachel J. van der Pol, Marije J. Smits, Michiel P. van Wijk, Taher I. Omari, Merit M. Tabbers, Marc A. Benninga. Efficacy of Proton Pump Inhibitors in Children With Gastro-Oesophageal Reflux Disease: A Systematic Review. *Pediatrics* 2011 May;127(5):925-935
9. Susan R. Orenstein, Eric Hassall, Wanda Furmaga-Jablonska, Stuart Atkinson, Marsha Raanan. Multicentre, DoubleBlind, Randomized, Placebo-Controlled Trial Assessing the Efficacy and Safety of Proton Pump Inhibitor Lansoprazole in Infants with Symptoms of Gastro-Oesophageal Reflux disease. *J Pediatr* April 2009;154(4):514-520
10. Davidson G, Wenzl TG, Thomson M, Omari T, Barker P, Lundborg P, Illueca M. Efficacy and safety of once daily esomeprazole for the treatment of Gastro-Oesophageal Reflux disease in neonatal patients. *J Pediatr*. 2013 Sep;163(3):692-8
11. Pezzati M, Filippi L, Psaraki M, Rossi S, Dani C, Tronchin M, Rubaltelli FF. Diagnosis of gastro-oesophageal reflux in preterm infants: sonography vs. pH-monitoring. *Neonatology* 2007;91(3):162-6
12. Siti Mazliah K, Norzila MZ, Deng CT, Zulfiqar A, Azizi BH. Prevalence, clinical predictors and diagnosis of gastro-oesophageal reflux in children with persistent respiratory symptoms. *Med J Malaysia*. 2000 Jun;55(2):180-7.
13. Johnston BT, Troshinsky MB, Castell JA, Castell DO. Comparison of barium radiology with oesophageal pH monitoring in the diagnosis of Gastro-Oesophageal Reflux disease. *Am J Gastroenterol*. 1996 Jun;91(6):1181-5.
14. Szajewska H, Hoekstra JH, Sandhu B. Management of acute gastroenteritis in Europe and the impact of the new recommendations: a multicenter study. *J Pediatr Gastroenterol Nutr* 2000 May;30(5):522-7.